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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	PAPER NUMBER
1646	#45

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/765,108	Krieger et al.
Examiner	**Art Unit**
Michael Brannock	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 10, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *11-15, 19-22, and 44-50* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *14 and 15* is/are allowed.

6) ☒ Claim(s) *11-13, 19-22, and 44-50* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Formal Issues:

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 39, 2/13/03, have been entered in full.

2. Claims 11-15, 19-22, and 44-50 are pending.

3. Applicant is notified that the restriction requirement set forth in Paper 31, 3/5/02, is hereby vacated.

4. Applicant is notified that the finality of the previous Office action has been withdrawn due to the issues raised below.

5. Applicant is notified that any objection or rejection of record that is not expressly repeated in Office action has been overcome by Applicant's response and withdrawn.

Information Disclosure Statement

6. Clarification of the record regarding the status of the Information Disclosure Statements (IDS) filed as Paper 11 (5/4/98) and as Paper 32 (4/11/02): The references cited in Paper 11 are identical to those of Paper 32. As set forth by the previous examiner at page 3, item VI, of Paper 31 (3/5/02), the IDS filed as Paper 11 was not considered because it was not in compliance

with 37 C.R.F § C.F.R. § 1.97(d); specifically it was filed after a Final Rejection but was not accompanied by a certification as specified in 37 C.R.F § C.R.F § 1.97(e), a petition and a petition fee. Further it did not contain copies of the documents cited therein (37 C.R.F § C.R.F § 1.98(d)(1) and it did not specifically identify that prior U.S. Patent Application from which priority is claimed and in which a copy of each of the recited documents can be found.

In response, at page 4 of Paper 35 (7/10/02), Applicant stated that an IDS with copies of all cited references and payment of the fee for filing after issuance of an office action was mailed in this case on March 29, 2002. The post card indicated receipt of the IDS by the USPTO on April 11, 2002. Thus, it appears that the IDS that was mailed by Applicant on March 29, 2002 is Paper 32. However, as of the date of this writing, only copies of several of the many references cited in Paper 11 and Paper 32 have been matched with the Application. Those references that have been received were considered by the previous examiner on 10/2/02 and a copy of Paper 32 was supplied with the Office action mailed 10/10/02 as Paper 36. It is noted that no explanation appears to have been provided in Paper 36 as to why the many references were not considered. This explanation is provided above, i.e., copies of the references were not matched to the application. Applicant is invited to supply copies of the remaining references for consideration by the Examiner.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 11-13, 19-22, 44-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons:

(a) Claims 11 and 50 and dependent claims 12, 13, 19-22 require, a "functional" scavenger receptor protein type BI (claim 11), or method comprising determining "the function" of scavenger receptor protein type BI (claim 50). As used in the art to describe a newly isolated protein that has been characterized in various in vitro assays, the word "function" is of dubious value in establishing and describing the sphere of biologic properties that a protein may have in an intact organism. The word "function" implies more than a list of physical properties, and is more akin to the idea of a biologic role for the protein. The instant specification has not set forth what aspects of the scavenger receptor protein type BI define its function or biologic role. The specification, at pages 29-30, merely hint at, and in a generalized way, potential biologic roles for the protein, e.g. that the data provide support "for the potential role of this receptor in lipoprotein and lipid metabolism", see page 29, Lines 19-20. In fact, the specification as filed (other than claim 50) does not appear to use the word "function" in relation to the scavenger receptor protein type BI. Thus, the artisan could not reasonably and unambiguously know wether or not he or she

was practicing the claimed invention, because he or she would not know what is meant by the term "function" or "functional" in relation to the claims.

(b) Claims 1-13, 19-22, 44-50 require a vast, and essentially limitless, number of proteins that are "scavenger receptor protein type BI" proteins, yet the claims do not set forth that element or combination of elements that is unique to or definitive of a "scavenger receptor protein type BI", as set forth previously in items 8 and 9 of Paper 36 (10/10/02) and further elaborated upon below.

(b1)Regarding the defining properties, on the claims, of the stringency conditions recited in the claims, Applicant argues that moderately stringent conditions are defined at page 10, lines 24-31, and that, essentially, the claims are definite because one would know how determine the melting temperature of a perfectly matched double stranded DNA molecule. This argument has been fully considered but not deemed persuasive. There appears to be a simple misunderstanding between Applicant and the examiner with regard to how the teachings at page 10 relate to the way the claims are currently worded. As currently worded, the melting temperature of the perfectly base-paired double stranded DNA provides the reference temperature with which the nucleic acid encoding the "scavenger receptor protein type BI" must hybridize, i.e. at 25°C below the melting temperature of the perfectly base-paired double stranded DNA. Thus, the melting temperature of the perfectly base-paired double stranded DNA determines the bounds of the claims. If, for example, the perfectly base-paired double stranded DNA were very long and have a high GC content, then it would have a higher melting

temperature than a perfectly base-paired double stranded DNA that was shorter or had less GC content. The higher the melting temperature of the reference perfectly base-paired double stranded DNA, the higher the hybridization temperature and thus the number of potential molecules that could hybridize to SEQ ID NO: 3 or 7 would diminish as the melting temperature increased. These facts are clearly articulated by the specification at pg 40, Lines 18-35. The problem with the claims is that they do not set forth *which* perfectly base-paired double stranded DNA *is* the reference polynucleotide. And nor do the claims or specification indicate that *any* perfectly base-paired double stranded DNA could serve as the reference DNA, as one skilled in the art would not expect that to be possible and would not consider that to be a reasonable interpretation of the claims. Thus, this is not a matter of a undue breadth, as argued by Applicant. Therefore, in the vast continuum of hybridization conditions required by the claims, it is unclear what conditions are meant to provide meaning and definitiveness to the phrase "scavenger receptor protein type BI". One of ordinary skill in the art would view the teachings of the specification at pg 40, Lines 18-35, as they relate to hybridization to SEQ ID NO: 3 or 7, to mean that the reference polynucleotide ***is*** a perfectly base-paired double stranded DNA consisting of SEQ ID NO: 3 or 7. Yet, this is not what is currently being claimed. See suggested claim language below.

(b2) Furthermore, claim 11 requires "moderately stringent conditions" whereas claim 13 requires "stringent" conditions, yet each recite that the conditions are that produced at a temperature of approximately 25°C below the melting temperature of the perfectly base-paired

double stranded DNA. Thus, it is unclear what difference is meant, if any, between the "moderately stringent conditions" of claim 11 and the merely "stringent" conditions of claim 13.

(b3) Additionally, claims 11, 44, 48 and 49 recite the limitation "which selectively binds to low density lipoprotein and to modified lipoprotein". This phrase is not sufficient, either alone, or in conjunction with the other limitations recited in the claims, to provide a meaningful definition of the phrase "scavenger receptor protein type BI". Further, the specification does not teach that these limitations are definitive of a "scavenger receptor protein type BI". At page 10, line 39 bridging page 11, the specification teaches that hsSR-BI differs from CD36 and other modified lipoprotein receptors described to date in that its binding of AcLDL is inhibited by native LDL. See suggested claim language.

9. It is suggested to Applicant that the following claim language would meet the requirements of 35 U.S.C. 112, second paragraph, as well as distinguish the claimed polynucleotides from those encoding CD36. Rejections under 35 U.S.C. 112, first paragraph, would, however, still apply.

Claim 11. An isolated nucleic acid molecule encoding a scavenger receptor protein type BI which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell media containing 10% serum, wherein the binding of AcLDL to said scavenger receptor protein type BI is inhibited by native LDL, and

which isolated nucleic acid molecule hybridizes to SEQ ID NO: 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly based-paired double stranded DNA molecule consisting of SEQ ID NO: 3 or 7.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 11-13, 19-22, 44-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding a polypeptide of either SEQ ID NO: 4 or 8, does not reasonably provide enablement for nucleic acids encoding a scavenger receptor type BI protein other than SEQ ID NO: 4 and 8. Nor does the specification provide an enabling basis for a compound that selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI, as required by claim 49. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, as set forth previously in item 6 of Paper 7, (6/26/97) and on page 4, item VIII (1), of Paper 31 (3/5/02) and elaborated upon below.

(a) The claims encompass an essentially limitless number of polynucleotides encoding polypeptide variants of the polypeptide of SEQ ID NO: 4 or 8, i.e. substitutions, deletions or

insertions in a protein corresponding to SEQ ID NO: 4 or 8; yet the specification has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 4 or 8, but which still retain a desired property of the polypeptide of SEQ ID NO: 4 or 8. The specification discloses two naturally occurring polynucleotides encoding scavenger receptor protein type BI proteins, which selectively bind to low density lipoprotein and to modified lipoprotein, from two species of rodents, yet the vast majority of polypeptides required by the claims are amino acid sequence variants of SEQ ID NO: SEQ ID NO: 4 or 8 - artificially produced versions of SEQ ID NO: 4 and 8 and naturally occurring allelic variants of SEQ ID NO: 4 and 8, as well as homologs of SEQ ID NO: 4 and 8 from other species, including allelic variants of those undisclosed species homologs. The specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, the specification has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 4 or 8 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 4 or 8 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 4 or 8 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 4 or 8, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the

protein corresponding to SEQ ID NO: 4 or 8. Conversely, if a protein variant of SEQ ID NO: 4 or 8 need not have a disclosed property, then the specification has failed to teach how to use such a variant.

(a) The specification has failed to teach how to make and use artificially constructed variants of SEQ ID NO: 4 or 8 without undue experimentation, as set forth previously in item 6 of Paper 7, (6/26/97), and recast and elaborated on below. Claims 11-13, 19-22 and 44-50 place very little in the way of structural limitations on the required scavenger receptor type BI protein. The claims are, in essence, single means claims, because the claims encompass any composition having the recited activities whereas the instant specification only discloses those two naturally occurring compositions known to the inventor, i.e. SEQ ID NO: 3 and 7. In *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a). With regard to enablement for artificially constructed variants of the polypeptides encoded by SEQ ID NO: 3 or 7, the instant fact pattern is actually one step deficient and removed from that

of *Hyatt*. The instant specification does not disclose any working examples of artificially constructed variants of the polypeptides encoded by SEQ ID NO: 3 or 7.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, the specification has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Further, although the specification mentions that various computer programs could be used in the search for important structural portions of the proteins, it is well recognized in the art that such programs are not sufficient to reliably predict the structural, let alone functional, aspects of a protein based on amino acid sequence, see Ngo et

al., in The Protein Folding Problem and Tertiary Structure Prediction (1993), Birkauser, Boston, pages 492-495.

Although the skilled artisan is aware of many art-recognized procedures for producing variants, as suggested at page 39, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, which there appears not to be, these may not be sufficient, as the skilled artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The specification has merely offered the skilled artisan an invitation to embark on a plan of essentially random trial and error experimentation, wherein in variants are produced by randomly selecting amino acids for substitution, deletion or insertion, and then testing these variants to try to find those that meet the limitations of the claims. Such experimentation is undue and would not be seen by one of skill in the art to be routine.

Thus, due to the large quantity of experimentation necessary to generate the infinite number of variants required by the claims and then to screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the

effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any meaningful structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

In Applicant's response of 2/13/03, Paper 39, Applicant does not appear to respond directly to this aspect (above) of the rejection, i.e. enablement for artificially produced variants.

(b) The specification has not provided an enabling disclosure for species homologs of SEQ ID NO: 3 and 7. The claims encompass, and claim 19 specifically requires, polynucleotides encoding scavenger receptor protein type BI proteins from other species. The specification discloses two cDNA sequences from closely related rodent species, however, the specification provides no more than an invitation to the skilled artisan to begin a research plan to try to identify polynucleotides from other species, particularly that of human (e.g. pg 38-40). The specification merely hints at, and in only a generalized way, that the skilled artisan could ~~the~~ use the disclosed polynucleotide sequences to screen cDNA libraries or genomic DNA libraries to obtain the required polynucleotides. The skilled artisan would immediately appreciate that such generalized instructions do not enable one skilled in the art to obtain the required polynucleotides. Specific information, not generalized suggestions, are required by the skilled artisan to obtain the claimed polynucleotides without considerable trial and error experimentation. Using the specification as a guide, the skilled artisan would additionally need to answer a multitude of questions that cannot be arrived at in a straight forward manner. It is very easy to make the statement that the cDNA and/or genomic libraries can be used to obtained the polynucleotide (e.g. pg 38), it is a wholly

different matter, however to discover which cDNA library to use or which genomic DNA library to use- or which tissues to use to make such a cDNA library, or how to make and screen a genomic DNA library that could be expected to yield a gene encoding a protein as large as that of the disclosed scavenger receptor protein type BI proteins. The difficulty in answering such questions is further compounded by the fact that the artisan is provided no specific teaching as to parts of the disclosed polynucleotides that should be used as probes and under what conditions should the probes hybridize in order to isolate the required polynucleotides away from the many related polynucleotides that would be expected to hybridize under moderately stringent conditions in libraries constructed from non-rodent species. At page 38, the specification merely indicates that specific "regions of interest" are those of the nucleotide sequence which encode regions of the protein conserved between different receptors; between the same receptors for different species; and with discrete regions of the receptor proteins, e.g. cytoplasmic region, transmembrane region, etc.. The skilled artisan would view these teachings as simply generalized advice and not the specific information required to make probes that can be used to find homologs from other species. Thus, the artisan might have the right library, and not know it because he has the wrong probes; conversely, the probes may be correct, if only he could find the correct tissues with which to make the library. The specification offers essentially no specific help in this regard. To the contrary, the specification attests to the complex and unpredictable state of this art. For example, the hamster cDNA was obtained from a library that was generated from a rare variant of CHO cells, var-261, based on the apparently novel polyanion binding

properties of the cells, yet it turned out that the cDNA that was isolated, and is now the subject of interest, was not responsible for this activity - which apparently still remains a mystery, see page 27. Further, the tissue specific expression of this mRNA appears to be complex and not well understood. While Northern analysis appeared to indicate that the mRNA was expressed in adipose tissues, western analysis suggested that it was not - and that a different polynucleotide must have cross-hybridized strongly with the probe in adipose tissues (see page 32, beginning at L25). Thus, the expression of this polynucleotide appears to be confusing enough in those tissues examined and disclosed in the instant specification - what might be found in a human, for example, is simply beyond reasonable extrapolation.

With regard to the construction of genomic DNA libraries, the skilled artisan appreciates that a gene encoding a protein of 509 amino acids, e.g. SEQ ID NO: 4, is likely to be contained on an extremely large section of the genome. Assuming that the human genome does contain a homolog of the rodent gene, the skilled artisan would not view the acquisition of the human gene as a simple matter of routine experimentation. To the contrary, the state of the art of cloning genomic mammalian DNA, at the time the invention was made, recognized that much labor and experimentation could be expected in the endeavor. In fact, the specification does not even appear to suggest any specific methodologies as to how this is to be accomplished, e.g. passing reference to the idea of genomic libraries is made at page 34, line 33, but no teachings follow. Sambrook et al, 1989 Molecular Cloning: A laboratory Manual, is cited at page 35. Sambrook et al. is recognized as a leading authority on molecular cloning at the time the instant Application

was filed. Beginning at page 9.5, Sambrook et al. review the state of the art regarding cloning of eukaryotic genes:

> "Although vectors based on bacteriophage λ have been extremely powerful tools for the isolation of both cDNA and genomic versions of many eukaryotic genes, they can only accommodate inserts that fall within a defined size range. Currently available bacteriophage λ vectors can accommodate inserts approximately 24 kb in size, and cosmid vectors can accommodate inserts of approximately 35-45 kb in length. In the past few years, it has become obvious that many genes are too large to be cloned as a single fragment from these vectors. For example, the gene for human factor VIII is 180 kb in length and the dystrophin gene is at least 1800 kb in length. Furthermore efforts to map and clone large segments of eukaryotic chromosomes have been hindered by the small size of the individual steps that can be achieved during chromosome walking".

In the Declaration filed 2/14/03 (Paper 43) Applicant argues that it was routine to screen genomic libraries using cDNA probes as much as a decade before the filing of the instant application. Applicant provides two examples wherein a gene was cloned from the corresponding cDNA of the same species and one example wherein a mouse gene was cloned using the human cDNA, i.e., Degrave, W. et al., Molec. Biol. Rep. 11(57-61)1986. One skilled in the art, at the time of filing of the instant application, would appreciate that the *technique* of library screening using probes designed from cDNA was routine in the art, as applicant suggests, in that it was done routinely by many laboratories, but the skilled artisan would not view the cloning of the entire coding sequence of a human gene using a hamster cDNA as routine. That this has been done and reported in the literature, and that the skilled artisan would think it would likely be *possible* for a

given hamster cDNA, does not make this endeavor routine - particularly regarding a protein as large as SEQ ID NO: 4, wherein extensive chromosomal walking would be expected. In *Enzo Biochem, Inc. v Calgene, Inc.* 188 F.3d 1362, 1371-72, 52 USPQ2d 1129, 1136 (Fed. Cir. 1999), it was noted that although Enzo attempted to admit post-trial evidence that included nearly one hundred technical articles which were offered at trial that described successful antisense experiments, the CAFC took the view that the district court's comprehensive opinion indicates that the court carefully considered a voluminous amount of competing evidence and testimony, and determined that the district court did not err in concluding that the generic claims directed to antisense technology in eukaryotic cells were nonenabled. The protein of interest in the Degrave, W. et al. article was only 153 amino acids in length, the entire gene fitting on a genomic fragment of only 11.5 kb (see col 1 of page 60) - well within the recognized limits of the cloning systems available (see above). The instant polypeptide of 509 amino acids would not be expected to fit so convenient. Cao, G., et al. J. Biol. Chem. 272(52)33068-33076, 1997, report the isolation of the entire human SR-BI gene. Using a state of the art human P1-derived artificial chromosome library, Cao, G., et al. found that the gene residing on a 120 kb fragment of genomic DNA (see col 1 of 33069); the gene, itself, was found to occupy approximately 75 kb. Thus, regardless of whether or not one skilled in the art would view the work of Degrave, W. et al. as being simply routine in the art (e.g. one may be reasonably sure that the authors of Degrave, W. et al. would not view it as such) the difference between the cloning problem presented to Degrave, W. et al. is qualitatively and quantitatively different than the cloning problem

confronted by Cao, G., et al., as it is also qualitatively and quantitatively different from the cloning problem presented to the highly skilled artisan who is trying to practice the invention as claimed.

Applicant argues, on page 6 of Paper 39, that methods to generate a genomic library are disclosed on page 34 and 35. This argument has been fully considered but not deemed persuasive. The examiner can find no teaching regarding genomic libraries anywhere in the specification.

Applicant argues, on page 6 of Paper 39, that the inventors have demonstrated constructive reduction to practice of the genomic DNA for SR-BI and the genomic DNA for SR-BI from different species. This argument has been fully considered but not deemed persuasive. The examiner can find no evidence, in either the instant specification, nor the Declarations filed 2/14/03 (Paper 43) and 1/5/1998 (Paper 9) of constructive reduction to practice of the genomic DNA encoding human SR-BI or any other species, although it should be pointed out that human gene became available with the publishing of Cao, G., et al. (supra) in 1997.

Applicant argues that the Declaration (Paper 43) indicates that methods were known in the art at the time of filing that would enable one to use the hamster cDNA to find homologs in other species. This argument has been fully considered but not deemed persuasive for the reasons detailed above. While it is certainly true that species homologs were ultimately be found, the mere invitation to conduct that research places an undue burden on the skilled artisan for the reasons detailed above.

Applicant's arguments regarding *Amgen Inc. v. Hoescht Marion Roussel, Inc.* are misplaced. That case was not concerned with enablement for undisclosed nucleic acids from other species, as is here, rather the issue was wether or not the claims were enabled for the use of known nucleic acid molecules in host cells from different species - and did not require that the artisan discover novel nucleic acid molecules. Thus, *Amgen Inc. v. Hoescht Marion Roussel, Inc*, does not appear to be relevant here.

At page 7 of Paper 39, Applicant argues that the submitted lab notebook pages provide support for using the hamster cDNA to screen a mouse genomic library and isolate the mouse SR-BI homologue with routine experimentation. This argument has been fully considered but not deemed persuasive, the examiner can find no mention of a genomic library.

(c) The specification does not provide an enabling basis for allelic variants of SEQ ID NO: 3 or 7. The clams encompass naturally occurring allelic variants of SEQ ID NO: 3 or 7, yet the specification failed to teach where to look for naturally occurring allelic variants of SEQ ID NO: 3 or 7, e.g. no specific disorder or specific phenotype has been asserted to correlate with a naturally occurring allelic variant, such that the artisan might know where to obtain a variant. The specification merely offers the skilled artisan the invitation to randomly try to find variants through trial and error sampling of animal populations. Such random trial and error experimentation is unduly burdensome.

(d) The specification does not provide an enabling basis for the administration of a compound that selectively inhibits binding of lipoprotein to the scavenger receptor protein type

BI, as required by claim 49, as set forth in item 7 of Paper 7. The specification provides no such compound, but merely an invitation to find such a compound, if such a compound can be found. One highly skilled in the art appreciates that the screening assays described on pages 43-54 are useful for determining whether or not a compound selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI; and although they are useful in the search for such compounds, they do not automatically produce the compounds. The invitation to use these assays to search for compounds having the desired properties is simply an invitation for further research and investigation to randomly sample any and all compounds for the desired activity. Such random experimentation is unduly burdensome. Applicant's arguments have been addressed in item 6 of Paper 10.

12. Claims 11-13, 19-22, 44-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a hamster and a mouse polynucleotide of SEQ ID NO: 3 and 7, respectively, yet the claims encompass polynucleotides not described in the specification, i.e. polynucleotides sequences from other species, mutated sequences, allelic variants, or sequences need that need only hybridize to SEQ ID NO: 3 or 7 under moderately stringent conditions yet which retain the required functional limitations. None of these sequences meet the

written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist or could exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide from hamster and a single polynucleotide from mouse, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, only two polynucleotide sequences, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

With the exception of the hamster and mouse polynucleotides referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed "scavenger receptor protein type BI" that are not encoded by SEQ ID NO: 3 or 7, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid

itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the hamster and mouse polynucleotides, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). Further, claim 49 requires a compound that selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI, there is no description of such a compound, and nor could one be envisioned based merely on a desired activity of the compound.

Citing *Enzo*, Applicant argues the written description requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular known structure. This argument has been fully considered but not deemed persuasive, the issue here is that the specification has not put forth a particular structure(s), present in each member of the vast and disparate genus claimed, that is asserted to correlate with a function. The mere recitation that the polynucleotide hybridize under moderately stringent conditions does not stipulate or describe any particular structure or function - it simply provides some constraint on

the possible deviation in structure that is allowed, although this constraint is fairly small when one considers that the hybridization conditions allow for an essentially limitless number of variants. Thus, regarding a structure/function correlation, there is no particular structure/function correlation between any variant of SEQ ID NO: 3 or 7 and any particular function.

As before, Applicant's reliance on *Amgen* is misplaced. That case was not concerned with undisclosed nucleic acids from other species, as is here, rather the issue was wether or not there was an adequate written description for host cells of other species that could be used to express the protein from known nucleic acid molecules - and it did not require that the artisan decide whether or not the Appellant was in possession of novel and unknown nucleic acid molecules. Asserted claims directed to production of recombinant erythropoietin are not invalid for failing to sufficiently describe all vertebrate and mammalian cells as engineered in claimed invention, even though precise definitions of DNA sequences are not disclosed, since terms "vertebrate"and "mammalian" are used to identify types of cells that can be employed to produce human recombinant EPO, not undescribed, previously unknown DNA sequences, and since terms therefore readily convey distinguishing information concerning their identity, such that one of ordinary skill in art could visualize or recognize identity of members of genus, page 1399, *[1 of 2] Amgen Inc. v. Hoechst Marion Roussel Inc.,* 65 USPQ2d 1385 (CA FC 2003).

Applicant argues that methods for obtaining the human DNA from genomic libraries are explicitly described on page 38, lines 13-20. This argument has been fully considered but not

deemed persuasive. As set forth previously, above, page 38 merely provides an invitation to the skilled artisan to try to find a human equivalent. These are generalized statements, no specific information about probes or libraries is given, and no information about genomic libraries is provided at all. Thus, the skilled artisan would not accept that Applicant was in possession of the information required to obtain a human polynucleotide encoding a scavenger receptor type BI protein.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

14. Claims 11, 13, 19, 20 and 22 rejected under 35 U.S.C. 102(a) as being anticipated by Calvo et al., J. Biol. Chem. 268(25)18929-18935, Sept. 05, 1993.

Figures 2 and 3 on pages 18931 and 18932 of Calvo provide the nucleotide sequences of a recombinant nucleic acid that Applicant has admitted is the human equivalent of the mouse and hamster SR-BI, e.g. the Declaration filed 1/5/98 (Paper 9), that would be expected to hybridize under the conditions of the claims, absent evidence to the contrary. Further the labeled nucleic acid of claim 20 can be found in Figure 5 on page 18993. Additionally, host cells comprising the

isolated nucleic acid (claim 22) were used in the cloning and sequencing of the nucleic acid, e.g. col 1 of page 18932.

Applicant argues that Calvo do not teach each and every feature of the claimed nucleic acid, e.g. that Calvo do not teach the function of the encoded protein. This argument has been fully considered but not deemed persuasive. What protein is encoded by the nucleic acid is an inherent and necessary part of that nucleic acid. The examiner can find no reason why the protein encoded by the nucleic acid disclosed by Calvo would not be the same as that claimed. Further, it is hard to reconcile applicant's arguments with Applicant's assertion that there was no need to isolate the human nucleic acid because Calvo had already published the protein sequence, see item 9 of the Declaration 2/13/02, Paper 40.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Calvo et al., J. Biol. Chem. 268(25)18929-18935.

Claim 21 requires an expression vector comprising the polynucleotide of claim 11. Although Calvo et al expressed the protein as a fusion with CD36 because antibodies to their new protein were not available (pg 18933, col 1), it would be obvious to one of ordinary skill in the art, i.e. a biomedical research scientist, to express the CLA-1 protein by incorporating the cDNA described therein into an expression vector and heterologous host by employing those methods which are routine in the art at the time the invention was made to permit the quantitative production of CLA-1 and to facilitate its characterization at the molecular level, particularly to conduct assays for binding partners of the polypeptide as suggested in col 2 page 1893 of Calvo, as would be commonly understood in the art.

Applicant's arguments regarding Calvo have been addressed above.

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. U.S. Patent No: 5,998,141 claim 10 was cited by the Board of Patent Appeals and Interferences as containing overlapping subject matter with that of the instant claim 11. The examiner finds that claim 10 of the 5,998,141 patent has no bearing on the claims of the instant application, i.e. the invention of claim 10 includes embodiments that are not encompassed by the instant generic claim 11, e.g. alleles that produce functionally defective or altered SR-BI proteins and which would not be obvious in view of the instant application, MPEP § 804 II 1a.

Conclusion

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

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July 11, 2003